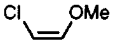
count the fact that 1,2-dimethoxyethene has two equivalent reaction sites, give free energy of activation differences of $\delta\Delta G^{\pm} = 5.6 \pm 0.1$ kcal mol^{-1} for the cis isomer and $\delta\Delta G^{\pm} = 6.2 \pm 0.1$ kcal mol^{-1} for the trans isomer. Each one of these is significantly greater than the double bond stabilizing effect of methoxy, $D = 5.2$ kcal mol^{-1}.[12] Such differences have been noted before, for dihydro-1,2-dioxin[3] and tetramethoxyethene;[4] it is likely that they are the result of an additional, transition-state destabilizing interaction produced by the electron-withdrawing polar effect of the methoxy group: this interacts unfavorably with the positive charge being generated on the substrate in these reactions.

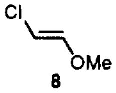
Cis–Trans Effects. The presently determined hydronium ion catalytic coefficients make *cis*-1,2-dimethoxyethene 2.9 times more reactive than its trans isomer. This difference is in the same direction as the difference in thermodynamic stability of the two substrates: equilibration experiments provide the equilibrium constant $K = 7.0$ for the trans-to-cis isomerization of the neat liquid olefins at 25 °C.[5] This equilibrium constant corresponds to the free energy difference $G_t - G_c = 1.15$ kcal mol^{-1}, which, when combined with the rate ratio $k_c/k_t = 2.9$, gives $G_t^{\ddagger} - G_c^{\ddagger} = 1.78$ kcal mol^{-1} for the difference in free energy between the cis and trans transition states.

It is not clear why *cis*-1,2-dimethoxyethene is more stable than its trans isomer, but the difference in stability of the transition states for the carbon protonation reactions would seem to have a straightforward explanation. The positive charge being generated on the substrates in this transition state will be delocalized onto a methoxy group oxygen atom and so will be displaced to one side of the (now partial) carbon–carbon double bond. The oxygen atom of the other methoxy group, being the negative end of a carbon–oxygen bond dipole, will then be able to interact more favorably with this positive charge when it is on the same side of the (partial) olefinic bond than when it is on the opposite side.

A similar reactivity difference has been found for *cis*- and *trans*-2-chloro-1-methoxyethene, 7 and 8. The cis



7



8

isomer here is 4 times more reactive to acid-catalyzed alcoholysis in ethanol solution than is the trans isomer.[13] The cis olefin is also the more stable isomer in this system.[14]

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No. 5, 7062-96-6; 6, 7062-97-7; D_2, 7782-39-0.

---

[13] Kankaanpera, A.; Salomaa, P.; Juhala, P.; Altonen, R.; Mattsen, M. *J. Am. Chem. Soc.* **1973**, *95*, 3618–3624.

[14] Okuyama, T.; Fueno, T.; Furukawa, J. *Tetrahedron* **1969**, *25*, 5409–5414.

Formation and Crystal Structure of 1-[*N*-Methylpyridoxylidenium]-2-[2′-*N*-methylpyridinium]hydrazine Diperchlorate and Its Red Tautomer[†]

Schelly Avramovici-Grisaru and Shalom Sarel*

Department of Pharmaceutical Chemistry, Hebrew University School of Pharmacy, P.O. Box 12065, Jerusalem 91120, Israel

Shmuel Cohen

Chemical Crystallography Unit, Hebrew University Institute of Chemistry, Givat-Ram Campus, Jerusalem, Israel

Received January 16, 1990

The isolation, characterization, and single-crystal structures of 1-[*N*-methylpyridoxylidenium]-2-[2′-*N*-methylpyridinium]hydrazine diperchlorate (**9**) (yellow, mp 258–259 °C) and of its red tautomer (**10**) (mp 215 °C) are herein described. Compound **9** was obtained from the reaction of an isomeric mixture of the respective monoiodides **5** and **6**, with 5% $HClO_4$; **5** and **6**, in turn, were formed in minor quantities in the reaction of 1-[pyridoxylidene]-2-[2′-pyridyl]hydrazine with a 4-fold excess of methyl iodide in boiling ethanol (48 h). The red isomer **10** was derived from **9** during its recrystallization. Whereas the crystals of the parent monomethylated diquaternary salt, 1-[*N*-methylpyridoxylidenium]-2-[2′-pyridyl]hydrazine diperchlorate (**2b**), are aligned in dimers through single $(O^2)\text{-}H\cdots N^{4'}$ contacts, those of **9** and **10** are monomeric. Their formation is rationalized in terms of cooperative hydrogen bonding.

Introduction

1-[Pyridoxylidene]-2-[2′-pyridyl]hydrazine (1) is a representative of a new generation of lipophilic chelators based on pyridoxal, which manifest high affinity for iron, oral activity, therapeutic safety, and high efficiency in removal of toxic accumulation of iron in transfusional iron overload.[1-3] Of the six distinctly different heteroatoms in 1,

---

[†] Dedicated to the memory of Professor David Ginsburg (deceased March 9, 1988).

[1] Sarel, S.; Grisaru, S.; Hershko, C.; Link, G.; Spira, D.; Iheanacho, E. *Trends in Medicinal Chemistry 88*; van der Goot, H., Domany, G., Pallos, L., Timmerman, H., Eds.; Elsevir Science Publishers: Amsterdam, 1989; pp 743–755.

0022-3263/90/1955-5236$02.50/0

Table I. ^{13}C NMR Data (δ, ppm) of 5, 6, 9, and 10 in DMSO-d_6

assignmt	5	6	9	10	carbon type
C(11)	158.7; 153.0	153.7	152.7	158.5	quaternary
C(4)		151.9; 148.5		146.9	quaternary
C(13)	142.8		144.2	170.5	quaternary
C(3)	142.3	143.8	142.9		quaternary
C(10)	141.1	141.2	142.5	142.0; 140.1	quaternary
C(12)	140.0	138.6	142.0	141.2	quaternary
C(2)	134.1	134.7	136.0	134.1	quaternary
C(5)	133.9	133.8	134.8	133.9	quaternary
C(1)	127.9	128.6	129.4		methine
C(14)		117.6	113.8	110.9	quaternary
C(9)	110.1; 110.9	108.1	112.0; 15.2	110.2; 69.9	
				58.0	methine
C(7)	58.0	58.4	58.8	58.3	methylene
C(6)	45.4	45.4	45.9	45.2	primary *N*-methyl
C(6)	(18.4)	(18.4)	42.0		primary *N*-methyl
C(8)	12.9	12.9	13.2	12.4	primary methyl

Table II. ^1H NMR Chemical Shift Data (δ, ppm, DMSO-d_6) of Prominent Protons in 1, 2a,b, 3, 5, 6, 9, and 10

compd	(C^6)-H	(O^1)-H	(C^1)-H	(C^9)-H	(C^{15})-H	(N^3)-H	(C^{14})-H	(C^{13})-H	($C^{12,11}$)-H
1		11.82	8.54	8.23		11.44	7.93	7.72	6.89
2a	4.27	12.50	8.46	8.44		8.46	8.29	7.80	6.99
2b	4.23	12.30	8.49	8.49		8.22	7.94	7.08	
3	4.22	12.11	8.47	8.31			7.79	7.04	5.89
5	4.22	13.35	8.60	8.38	3.76				
6	4.19	13.25	8.46	8.30	3.99				
9	4.27		8.93	8.58	3.76		8.15	7.68	7.18
10	4.22; 4.19		8.61	8.39			8.04	7.76	7.19; 6.66

only the azomethinic nitrogen (N^2), the pyridinic ring nitrogen (N^4), and the phenolic oxygen (O^1) function as sites for metal coordination. The other three (N^1, N^3, and O^2) play key roles in hydrogen contacts, determining geometrical patterns of hydrogen bonding.

The groups HN^1 and HN^3 act exceptionally as two-center acceptors,[4] whereas the primary alcohol group (O^2)-H acts typically both as symmetrical three-center[5-7] acceptor and donor. Quaternization of the pyridoxylidene ring nitrogen (N^1) in 1 was shown[2] to enhance not only the mobilization of iron from the body but also to favor its excretion through the urine rather than through the feces.[8]

In a recent publication[9] the formation of 3 was rationalized in terms of cooperative[10] hydrogen bonding of the (O^2)-H group, causing stabilization of long-chain contacts in the resulting supramolecule. We deemed it interesting to establish whether or not this enhancing effect prevails if a second methyl group is placed on the other pyridinic nitrogen (N^4), which otherwise functions as a potential coordination site in iron binding. Toward this end we sought to secure the di-N-methylation product 4 by allowing 1 to react with a 4-fold excess of methyl iodide in boiling ethanol for 48 h. Study has revealed that although the initial stage of the reaction (1) → 2 [N^1-methylation] is facile, the successive one [2 → 4, N^4-methylation] is rather sluggish. Thus, after 48 h of reaction only 10–15% 2 → 4 conversion could be observed. In our hands, the expected dimethiodide 4 could not be isolated, apparently because of its great tendency to undergo dehydroiodination reaction to yield the respective N^1,N^4-dimethyl monoiodide products [4 → 5 + 6].

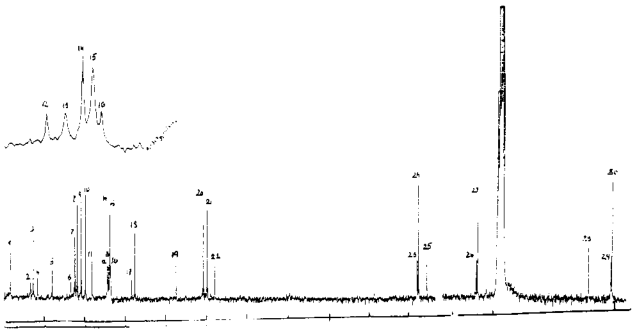


Figure 1. ^{13}C NMR spectra of red product (mp 277–278 °C) in DMSO-d_6 attributable to an isometric mixture of structures 5 and 6.

The latter (red crystals, mp 277–278 °C) is shown to be an isomeric mixture of structures 5 and 6, since on reaction with 5% $HClO_4$ it transforms into a single yellow crystalline product (mp 258 °C) of structure 9. In solution (EtOH, DMSO), or in the solid state on daylight, the yellow diperchlorate 9 transforms very slowly into a red isomeric diperchlorate of mp 215 °C, to which structure 10 was assigned.

Experimental Section

Compound 1 was obtained as described.[9] ^1H and ^{13}C NMR spectra were obtained on Varian VXR 300 spectrophotometer, with TMS as an internal standard and Me_2SO-d_6 as solvent. Ultraviolet spectra were run on a Kontron Uvikon 810 spectrophotometer. Mass spectra were recorded with a LKB 21 spectrometer.

N^1,N^4-Dimethylation of 1. Formation of 1-[*N*-Methylpyridoxylidenium]-2-[2′-pyridyl]hydrazine Iodide (2) and 1-[*N*-Methylpyridoxylidenium]-2-[2′-*N*-methylpyridinium]hydrazine Iodides [5 + 6]. The free base 1 (0.93 g, 3.5 mmol) in dry ethanol (100 mL) was allowed to react with

---

(2) Sarel, S.; Avramovici-Grisaru, S.; Hershko, C.; Link, G.; Spira, D., 1989, EP 0315434 A2.

(3) (a) Hershko, C.; Link, G.; Pinson, A.; Sarel, S.; Grisaru, S.; Hasin, Y.; Grady, R. W. In *Trace Elements in Man and Animals* 6; Hurley, L. S., Keen, C. L., Lonnerdal, B., Rucker, R. B., Eds.; Plenum Press: New York, 1988; pp 67–71. (b) Hershko, C.; Weatherall, D. J. In *Crit. Rev. Clin. Lab. Sci.* **1988**, *26*, 303–345.

(4) Jeffrey, G. A.; Maluszynska, H. *Int. J. Biol. Macromol.* **1982**, *4*, 173.

(5) Taylor, R.; Kennard, O. *Acc. Chem. Res.* **1984**, *17*, 320.

(6) Jeffrey, G. A.; Mitra, J. *J. Am. Chem. Soc.* **1984**, *106*, 5546.

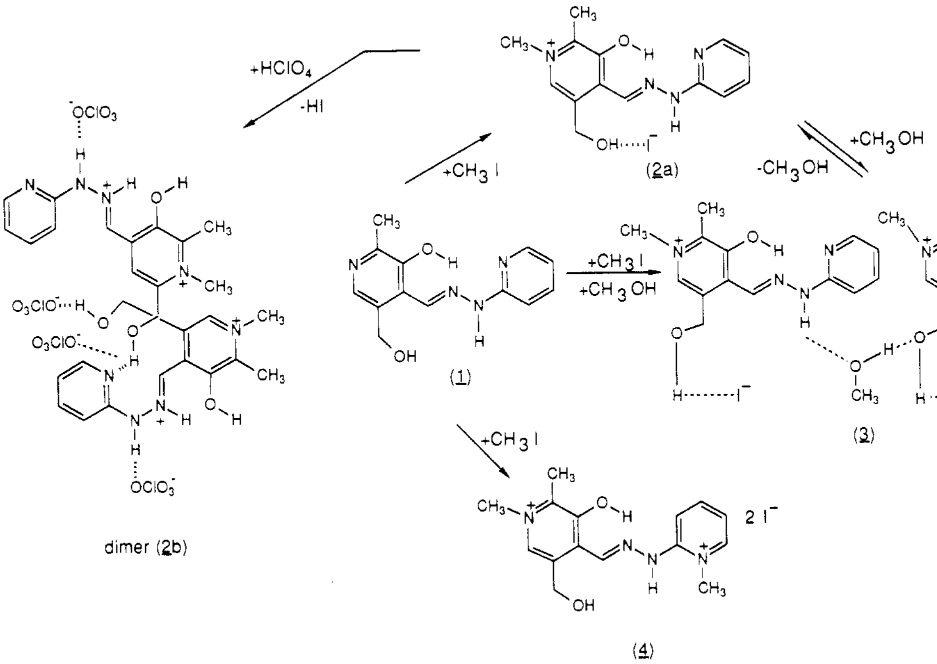
(7) Taylor, R.; Kennard, O.; Versichel, W. *J. Am. Chem. Soc.* **1984**, *106*, 244.

(8) The spontaneous excretion of radioiron (^{59}Fe) in the urine and in the feces of normal rats (within 4 days of injection subcutaneously) is dramatically enhanced on treatment with the iron chelators 1–3: from 16.6% (urine) + 17.5% (feces) in the case of 1 to 39.0% (urine) + 27.0% (feces) in the cases of 2 and/or 3.[1-3]

(9) Avramovici-Grisaru, S.; Cohen, S.; Sarel, S. *Heterocycles* **1990**, *30*, 1079.

(10) Del Bene, J. E.; Pople, J. A. *J. Phys. Chem.* **1970**, *52*, 4858.

Scheme I



a 4-fold excess of methyl iodide (2 g, 14 mmol) over 48 h at 78 °C. Removal of excess reagent and solvent provided an orange precipitate (1.1 g) comprising a mixture of 2 and [(*5*) + (*6*)] in a ratio of 5.5 to 1.0. Repeated recrystallization effected separation between the yellow methiodide **2a** (major) and the red isomeric mixture of di-N^1-,N^4-methylated iodides [**5** + **6**] (minor). Compound **2a** was converted into its corresponding diperchlorate **2b** with the aid of 5% $HClO_4$. The properties and crystall structures of **2b** and **3** (see Scheme I) have already been described.[9] Recrystallization of [**5** + **6**] from ethanol afforded red prismatic needles, mp 276–277 °C (mp 271–272 °C from MeOH). λ_{max} (MeOH): 466.9 nm (log ε 4.41), 344.8 (3.76), 339.6 (3.78), 267.9 (4.00), 219.3 (4.40). Its ^{13}C NMR decoupled spectrum exhibited 30 signals attributable to a mixture of **5** and **6** (see, Figure 1 and Table I). Table II presents the typical ^1H NMR resonances assigned to **5** and to **6**. MS: m/z = 287 (M^+ − I, 20), 179 ($C_9H_{11}N_2O_2^+$, 95), 163 ($C_9H_{11}N_2O^+$, 85), 109 ($C_6H_9N_2^+$, 100). Anal. Calcd for $C_{15}H_{19}N_4O_2$: C, 43.47; H, 4.59; N, 13.53; I, 30.68. Found: C, 43.28; H, 4.31; N, 13.09; I, 31.20.

Conversion of [5 + 6] into the Corresponding Diperchlorate (9). Isolation of a Red Tautomer (10). When the red crystals of [**5** + **6**] were added to a 5% $HClO_4$ solution, an immediate change in color with concomitant dissolution was noted. On short standing at room temperature, a yellow product emerged, which on recrystallization from ethanol provided crystals of 1-[*N*-methylpyridoxylidenium]-2-[2′-*N*-methylpyridinium]hydrazine diperchlorate (**9**), mp 258–259 °C. λ_{max} (MeOH): 468 nm (4.74), 341 (4.05), 339 (4.06), 267.5 (4.23), and 207.8 (4.47). ^1H NMR: δ 8.93 (1 H, s, C*H*—N), 8.58 (1 H, s, ring CH=N), 8.15 (1 H, t, *J* = 4.8 Hz, pyridinic 12-H), 7.63 (1 H, d, *J* = 1.8 Hz, 9-H), 7.18 (1 H, t, *J* = 0.4 Hz, 10-H), 4.88 (2 H, s, CH_2), 4.27 (3 H, s, N^1-CH_3), 3.99 (3 H, s, N^4-CH_3), 2.68 (3 H, s, CH_3). The ^{13}C NMR data of **9** are given in Table I. The elementary analysis of **9** was not attempted (explosion). Its composition was inferred from crystal analysis (see Figure 1 and Table V). Removal of solvent from the mother liquor by evaporation to dryness left a mixture of well-defined and distinctly different yellow **9** and red crystals, which were amenable to mechanical saparation (by hand). Red needles (minor), mp 215 °C. λ_{max} (MeOH): 500 nm (2.53), 394.9 (4.53), 341.1 (4.01), 339.6 (4.03), 299.4 (3.82), 244.9 (4.29), 215.0 (4.28). ^{13}C NMR: δ 170.5, 158.49, 147.87, 146.37, 142.23, 141.20, 140.14, 134.11, 133.88, 110.91, 110.0, 69.94, 58.33, 57.97, 45.22 and 12.43 (compare, Table I). ^1H NMR: 8.61 (1 H, s, CH=N), 8.39 (1 H, s, ring CH=H), 8.04 (1 H, d, *J* = 0.6 Hz, 12-H), 7.76 (1 H, m), 7.19 (1 H, m), 4.77 (2 H, s, CH_2), 3.76 (3 H, s, N^4CH_3), 2.65 (3 H, s, CH_3) (compare, Table II).

Crystal Data. Compound 9. Space group $P_{2_12_12_1}$, $[C_{15}H_{20}N_4O_2]^{2+}$ $2ClO_4^-$, M_r = 487.3, a = 11.633 (3), b = 23.967 (5), and c = 7.749 (2) Å, V = 2160.5 (7) Å^3, Z = 4, ρ_{calcd} = 1.50 g cm^{-3}, μ(Mo Kα) = 3.07 (cm^{-1}, no. of unique reflections = 2118, reflections with $I \geq 3\sigma(I)$ = 1213, R = 0.134, unit weights were used.

Compound 10. Space group $P_{2_12_12_1}$, $[C_{15}H_{20}N_4O_2]^{2+}$ $2ClO_4^-$, M_r = 487.3, a = 14.164 (5), b = 17.868 (5), and c = 8.281 (2) Å, V = 2095.8 (8) Å^3, Z = 4, ρ_{calcd} = 1.54 g cm^{-3}, μ(Mo Kα) = 3.16 cm^{-1}, no. of unique reflecitons = 1576, no. of reflections $I \geq 3\sigma(I)$ = 1130, R = 0.079, unit weights were used.

X-ray Crystal Structure Analysis. Data were measured on a PW1100/200 Philips four-circle computer-controlled diffractometer. Mo Kα (λ = 0.71069 Å) radiation with a graphite crystal monochromator in the incident beam was used. The unit cell dimensions were obtained by a least-square fit of 20 centered reflections in the range of 10° ≤ θ ≤ 13°. Intensity data were collected by using the ω–2θ technique to a maximum 2θ of 46°. The scan width, $\Delta\omega$, for each reflection was 1.00 + 0.35 tan θ with a scan speed of 0.05 deg/min. Background measurements were made for a total of 20 s at both limits of each scan. Three standard reflections were monitored every 60 min. No systematic variations in intensities were found. Intensities were corrected for Lorenz and polarization effects. All non-hydrogen atoms were found by using the results of the SHELXS-86 direct method analysis.[11] After several cycles of refinements[12] the positions of the hydrogen atoms were calculated and added with a constant isotropic temperature factor of 0.05 Å^{12} to the refinement process. Refinement proceeded to convergence by minimizing the function $\sum w(|F_o| - |F_c|)^2$. A final difference Fourier synthesis map showed several peaks less than 0.5 e/Å^3 scattered about the unit cell without a significant feature. The discrepancy index $[R = \sum[|F_o| - |F_c|]/\sum|F_o|$.

The equivalent isotropic B's were calculated from the equation $B_{eq} = (^8/_3)\pi^2(u_{11} + u_{22} + u_{33})$. Tables of atomic coordinates and the isotropic B equivalents of thermal parameters are given in Tables III and IV. Additional bond lengths and angles, anisotropic temperature factors, and thermal parameters are available from the author.

Results and Discussion

The assignment of an isomeric mixture, probably of structures **5** and **6**, to the red minor product emerging from the reaction of **1** with CH_3I followed (i) from its elementary analysis; (ii) its ^{13}C NMR spectrum (Figure 1); (iii) its conversion into **9** upon reaction with 5% $HClO_4$ (Scheme

---

[11] Sheldrick, G. M. *Crystallographic Computing 3*; Oxford University Press: 1985; pp 175–189.

[12] All crystallographic computing was done a Cyber 855 computer at the Hebrew University of Jerusalem, using the SHELX 1977 structure determination package.

Scheme II

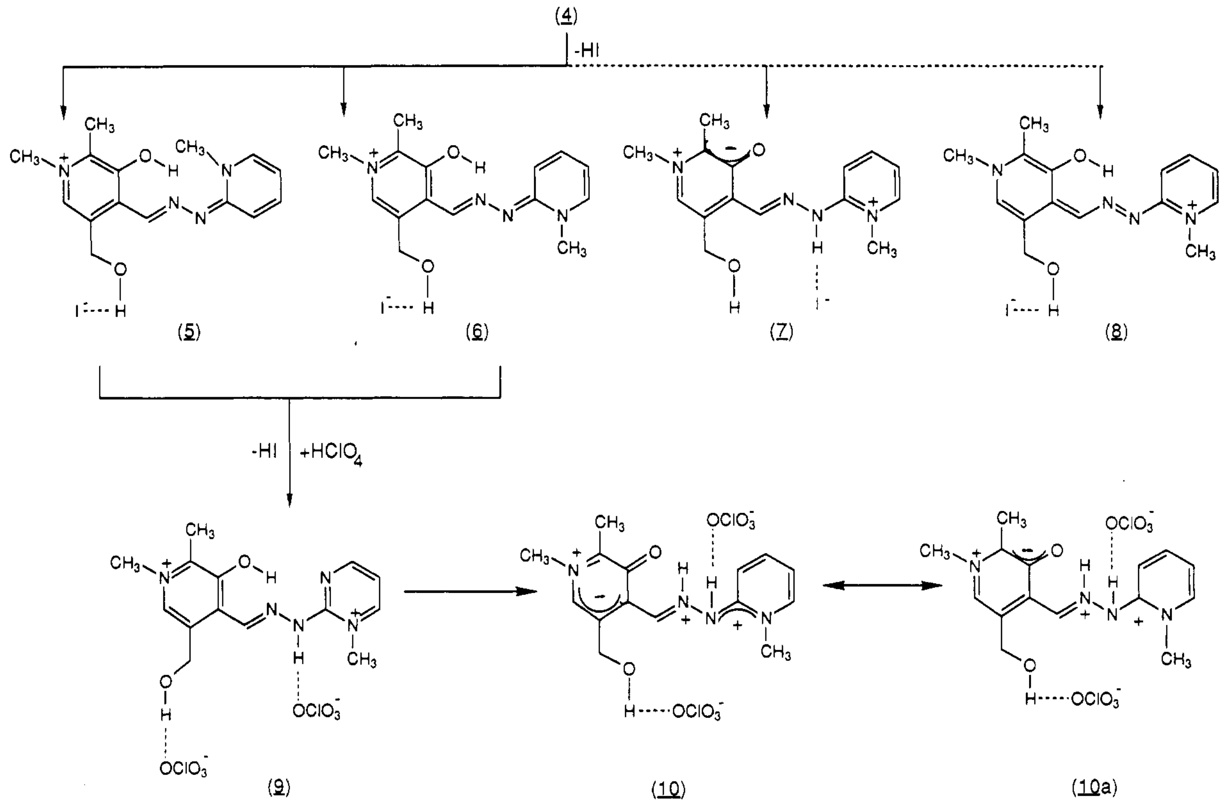


Table III. Positional Parameters and Isotropic Equivalent *B* Parameters of 9 (with Esd's in Parentheses)

atom	*x*	*y*	*z*	*B* (A²)
O(1)	1.1329 (7)	0.5440 (6)	0.5440 (6)	4.7 (2)
O(2)	1.2731 (9)	0.7931 (6)	0.539 (1)	6.2 (3)
N(1)	1.3427 (8)	0.5997 (6)	0.293 (1)	3.5 (2)
N(2)	1.0010 (8)	0.6351 (6)	0.188 (1)	3.7 (2)
N(3)	0.9127 (8)	0.6652 (7)	0.175 (1)	4.2 (2)
N(4)	0.7555 (8)	0.6528 (7)	0.100 (2)	4.3 (2)
C(1)	1.317 (1)	0.6621 (8)	0.370 (2)	3.9 (3)
C(2)	1.228 (1)	0.6881 (8)	0.361 (2)	3.6 (3)
C(3)	1.1611 (9)	0.6494 (8)	0.266 (2)	3.6 (3)
C(4)	1.1907 (9)	0.5839 (8)	0.189 (2)	3.5 (3)
C(5)	1.2840 (9)	0.5586 (7)	0.203 (2)	3.3 (3)
C(6)	1.443 (1)	0.5769 (9)	0.303 (2)	5.0 (3)
C(7)	1.198 (1)	0.7614 (9)	0.445 (2)	5.0 (4)
C(8)	1.314 (1)	0.4876 (8)	0.124 (2)	4.4 (3)
C(9)	1.0646 (9)	0.6766 (8)	0.252 (2)	3.5 (3)
C(10)	0.8398 (9)	0.6187 (8)	0.139 (2)	3.2 (2)
C(11)	0.678 (1)	0.6073 (9)	0.067 (2)	5.4 (4)
C(12)	0.683 (1)	0.535 (1)	0.074 (2)	6.4 (5)
C(13)	0.768 (2)	0.499 (1)	0.113 (3)	7.7 (6)
C(14)	0.847 (1)	0.5424 (9)	0.148 (2)	5.3 (4)
C(15)	0.741 (2)	0.740 (1)	0.091 (3)	8.5 (6)
Cl(1)	0.9519 (3)	0.8760 (2)	0.1928 (6)	4.3 (2)
Cl(2)	0.5358 (3)	0.3423 (3)	0.2284 (5)	5.2 (2)
O(11)	0.983 (1)	0.9442 (9)	0.141 (2)	11.0 (8)
O(12)	0.858 (2)	0.885 (1)	0.220 (4)	17.9 (2)
O(13)	0.968 (1)	0.8244 (8)	0.074 (2)	9.9 (1)
O(14)	0.985 (2)	0.856 (1)	0.317 (3)	21.9 (6)
O(21)	0.533 (2)	0.364 (2)	0.074 (2)	16.3 (2)
O(22)	0.497 (2)	0.395 (1)	0.324 (2)	17.0 (2)
O(23)	0.630 (1)	0.3294 (9)	0.274 (2)	9.9 (1)
O(24)	0.485 (2)	0.279 (1)	0.244 (4)	18.6 (2)

Table IV. Positional Parameters and Isotropic Equivalent *B* Parameters of 10 (with Esd's in Parentheses)

atom	*x*	*y*	*z*	*B* (A²)
O(1)	0.552 (1)	0.4077 (6)	0.019 (3)	6.1 (4)
O(2)	0.152 (2)	0.5185 (9)	0.060 (3)	9.5 (6)
N(1)	0.285 (2)	0.3423 (8)	−0.043 (3)	4.9 (4)
N(2)	0.525 (1)	0.5155 (6)	−0.013 (3)	3.9 (3)
N(3)	0.559 (1)	0.5707 (7)	−0.026 (3)	4.3 (4)
N(4)	0.699 (2)	0.6385 (8)	0.014 (3)	5.3 (5)
C(1)	0.215 (2)	0.388 (1)	−0.066 (3)	5.2 (6)
C(2)	0.256 (2)	0.4394 (9)	−0.062 (3)	4.7 (5)
C(3)	0.372 (2)	0.4499 (9)	−0.030 (3)	4.8 (5)
C(4)	0.446 (2)	0.4034 (9)	−0.014 (4)	4.9 (5)
C(5)	0.396 (2)	0.348 (1)	0.009 (4)	5.9 (6)
C(6)	0.237 (3)	0.286 (1)	−0.048 (5)	7.5 (7)
C(7)	0.164 (2)	0.488 (1)	−0.092 (4)	6.5 (7)
C(8)	0.470 (3)	0.300 (1)	0.034 (5)	8.7 (8)
C(9)	0.419 (2)	0.5057 (9)	−0.052 (3)	4.7 (5)
C(10)	0.667 (2)	0.5824 (9)	−0.009 (4)	5.0 (5)
C(11)	0.815 (2)	0.653 (1)	0.009 (5)	6.9 (5)
C(12)	0.895 (3)	0.615 (1)	0.035 (5)	8.7 (8)
C(13)	0.865 (3)	0.560 (1)	0.040 (4)	7.3 (7)
C(14)	0.760 (2)	0.544 (1)	−0.014 (4)	6.5 (6)
C(15)	0.608 (2)	0.6794 (9)	0.017 (4)	6.6 (6)
Cl(1)	0.7619 (5)	0.8392 (2)	0.036 (1)	3.9 (2)
Cl(2)	0.8728 (6)	0.8748 (3)	−0.000 (1)	6.3 (3)
O(11)	0.722 (6)	0.870 (2)	0.135 (6)	20.3 (4)
O(12)	0.802 (3)	0.794 (1)	0.122 (5)	13.9 (2)
O(13)	0.332 (3)	0.642 (1)	0.084 (5)	13.7 (3)
O(14)	0.187 (4)	0.673 (1)	0.069 (5)	16.8 (2)
O(21)	0.958 (2)	0.347 (1)	0.075 (9)	29.2 (2)
O(22)	0.882 (5)	0.414 (1)	−0.121 (4)	18.7 (3)
O(23)	0.797 (2)	0.341 (1)	−0.02 (2)	41.6 (2)
O(24)	0.857 (8)	0.395 (2)	0.121 (4)	35.3 (2)

II). On the basis of its ultraviolet–visible absorption spectrum with a band at 466.9 nm, structure 8 (a "dihydropyridine" belonging to a class of compounds called pyridine methenes[13]) could not be ruled out. Abbot and Bobrick[14] isolated a bright red compound from a reaction of diethylamino malonate and pyridoxal, which was assigned a dihydropyridine structure on the basis of an absorption maximum at 465 nm, which was taken to indicate a longer π electron system than is present in normal Schiff bases. However, according to Martell et al.,[15] a dihydro-

---

[13] Eisner, U.; Kuthan, J. *J. Chem. Rev.* **1972**, *72*, 1.

[14] Abbott, E. H.; Bobrick, M. A. *Biochemistry* **1973**, *12*, 846.

Table V. Intramolecular $RO^1 \bullet\bullet\bullet N^2$ Distances (Å) and Dihedral Angles (deg) between Planes 1,2,[a] 1,3,[c] and 2,3[b] in 2b, 3, 9 and 10

distances	compounds **2b**	 3	 9	 10
$RO^1 \cdots N^2$	2.80 (4)	2.53 (2)	2.60 (2)	2.61 (5)
$RO^2 \cdots I$		3.550		
$RO^2 \cdots OClO_3$	2.85		3.15 (6)	3.18 (4)
$RO^3 \cdots O^2$		2.92 (4)		
$RN^3 \cdots OClO_3$	2.92, 3.23		3.06 (9)	3.02 (3)
$RN^3 \cdots OCH_3$		2.79 (5)		
dihedral angles between planes				
1,2	37.98	0.92	34.15	7.45
1,3	18.25	2.19	11.51	7.98
2,3	20.11	2.31	23.00	15.43

[a] Plane 1 includes N^1, C^{1-9}, O^1, O^2. [b] Plane 2: N^4, C^{10-15}, N^3. [c] Plane 3: C^3, C^9, N^2, N^3.

pyridine structure (8) should absorb above 500 nm, as has been observed for the quinonoid intermediate between 2-aminobutanoic acid and *N*-methanopyridoxal chloride,[16] which absorbs at 514 nm.[17] The keto isomeric structure 7 could not be substantiated by ^{13}C NMR spectroscopy (no absorption around δ 170), whereas those of 5 and 6 are in consonance with the ^{13}C NMR data (see Table I).

In parallel to N^1-methiodide (**2a**), which generates the corresponding diperchlorate salt (**2b**) on reaction with 5% $HClO_4$, the reaction of the red isomeric mixture [5–6] similarly with 5% $HClO_4$ afforded a single well-defined yellow crystalline diperchlorate of structure **9**. Unlike **2b**, which is dimer[9] (see Figure 6) involving a single (O^2)-H$\cdots N^{4\prime}$ contact (1.84 Å) within the dimer, **9** is monomeric. Interestingly, the dication frameworks both in **2b**[18] and **9** are bent, forming, respectively, 38 °C and 34 °C dihedral angles between the two heteroaromatic ring planes (see, Tables V and VI and Figure 6). Comparative study reveals that on going from **2b** to **9**, both the geometrical patterns of H contacts and the acceptor atoms and the distribution of the corresponding hydrogen-bond lengths vary significantly. Thus, the asymmetry in the "three-center bond" type[4,5] of both contacts of (N^3)—H$\cdots OClO_3$ and of (O^2)-H$\cdots OClO_3$ increase respectively from 1.92 and 2.23 Å, and 1.85 Å in **2b** to 2.07 and 2.35 Å, and 1.99 and 2.16 Å in **9**.[20] These lengthenings of the primary H$\cdots$O contacts are indicative of marked depletion of electron density, resulting from N^1,N^4-dimethylation. On the other hand, lessening of electronegativities both at N^1 and N^4 atoms entail shortening of intramolecular H-bond distances (O^1)—H$\cdots N^2$ by a quantity of ca. 0.2 Å (see Table V).

Oddly, complete evaporation of the mother liquor left after recrystallization of **9** (from ethanol) afforded a few red needles, melting at 215 °C, along with yellow crystals (predominant) of mp 258–259 °C (**9**). The red crystals were amenable to X-ray analysis, shown to be an isomeric form **10** of **9**.

Looking at ORTEP drawings of **9** (Figure 2) and **10** (Figure 4) reveal only minor differences in their molecular dispositions. However, the perspective view of **9** is bent, assuming a 34.15° dihedral angle between the two heteroaromatic ring planes (see Table V). In **10**, the corresponding dihedral angle is only 7.45° and as a consequence the dication framework appears almost flattened. Another relevant distinction refers to the alcoholic hydroxyl (O^2)-H group, which is in-plane in **9**, orienting away of the azomethinic moiety, but is out-of-plane in **10**, pointing toward the azomethinic group. These affect the dispositions of the two counterions around the dication frameworks. Thus, in **9** the bend framework is capable of accommodating the two counterions (ClO_4) on the same side of the dication, pointing toward the (O^2)-H and the (N^3)-H groups, whereas in **10** this is not the case. The conclave produced by the conformation of the (O^2)-H group is capable of accommodating a single ClO_4 anion only, pushing the second ClO_4 anion to assume an opposite disposition as shown in Figure 5. Sterically, flattened molecules such as **10** require a lesser space in the lattice than the respective bended molecules in the lattice of **9**. The ultraviolet-visible absorption spectrum of **10** exhibits a weak band at 500 nm, indicating a longer π electron system than present in **9**.

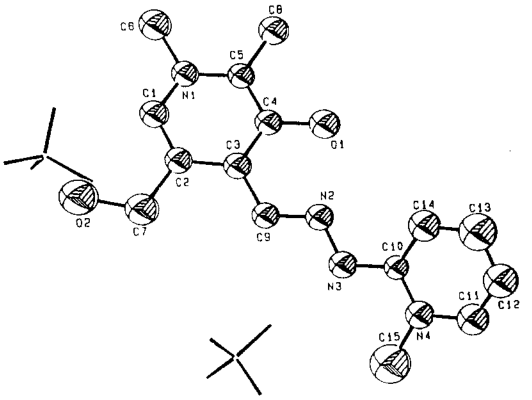


Figure 2. ORTEP drawing of **9** with the atom-numbering scheme and thermal ellipsoids at the 50% probability level.

Significantly the O(1)–C(4) distance of 1.27 Å, and both the O^1–C^4–C^5 angle of 116 (2)° and O^1–C^4–C^3 angle of 123 (2)° in **10** resemble the average C–O distance of 1.26 Å and the R–C–O angle ≈ 117.5° in carboxylic anions.[20] The N(3)–C(10) distance of 1.29 Å in **10** indicates that atom N(3) is sp^2-hybridized (plane-trigonal). This suggests a zwitterionic (betaine) structure[21,23] for the *N*-methyl-

---

[15] Sala, L. F.; Martell, A. E.; Motekaitis, R. J.; Abbott, E. H. *Inorg. Chem. Acta* **1987**, *135*, 123.

[16] Jenkins, W. T.; Hareff, R. C. *Org. Magn. Reson.* **1976**, *8*, 548.

[17] Karube and Matsushima (Karube, Y.; Matsushima, Y. *J. Am. Chem. Soc.* **1977**, *99*, 7356) have shown that when 2-aminobutanoic acid is replaced by 2-aminobutenoic acid the absorption shifts to 550 nm, in accordance with its more extended conjugation.

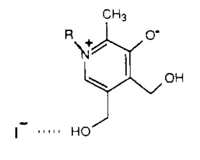
[18] Figure 6[19] depicts the alignment of the bend molecule of **2b** in the lattice of the dimer, underlining the differences both in orientation and plane dispositions of the (N^3)-H$\cdots OClO_3$ and (O^2)-H$\cdots OClO_3$ contacts in the two electronically different bend molecules, **2b** and **9**.

[19] The crystal data of **2b** are reported in ref 9.

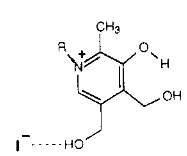
[20] (a) Speakman, J. C. *Structure Bonding* **1972**, *12*, 148. (b) Novak, A. *Structure Bonding* **1974**, *18*, 177 (Springer-Verlag, Heidelberg).

[21] The four absorption maxima at 341.1, 339.6, 299.4, and 244.9 nm in the spectrum of the red isomer are attributed to the betaine (zwitterionic) structure of the *N*-methylpyridoxylidenium moiety.[22]

[22] On the basis of absorption variation in the spectrum of pyridoxine with pH, Harris et al. (Harris, S. A.; Webb, T. J.; Folkers, K. *J. Am. Chem. Soc.* **1940**, *62*, 3198) assigned the two absorption maxima in H_2O at 330 and 256 nm to the zwitterionic structure 11 and the single one at 295 nm to the pyridoxine methiodide (tertiary base) (12).



(11)



(12)

[23] Similar O(1)–C(4) distances of 1.31 Å[24] to 1.30 Å[25–27] and O^1–C^4–C^5 angles of 116.6 (4)°[24,25] to 115.5 (4)°[26] and O^1–C^4–C^3 angles of 124.9 (9)°,[24] 126.5 (4)°,[25] and 123°[26] have already been observed in crystals of 1-[pyridoxylidene]-2-[*N*-isonicotinoyl]hydrazine[24] and of 1-[pyridoxylidene]-2-[*N*-salicyloyl]hydrazine[25] coordinated to iron(III),[24] copper(II),[25] and in Schiff-base chelates of pyridoxylidenevaline with Mn(II)[26] and Ni(II).[27]

Table VI. Torsional Angles (deg) for Chains of Four Atoms in 2a, 3, 9, and 10

chain of four atoms	**2a** (dimer)	**3** (long-chain supramolecule)	**9** (yellow isomer)	**10** (red isomer)
C(15)-N(4)-C(10)-N(3)			1.8 ∓ 2.1	0.3 ∓ 4.0
C(14)-C(10)-N(3)-N(2)	169.2 ∓ 1.1	178.1 ∓ 0.5	13.9 ∓ 2.1	14.5 ∓ 4.2
C(10)-N(3)-N(2)-C(9)	168.8 ∓ 1.2	179.6 ∓ 0.5	-166.9 ∓ 1.3	-171.9 ∓ 2.4
N(2)-C(9)-C(3)-C(4)	-18.4 ∓ 1.8	1.6 ∓ 0.8	10.6 ∓ 2.1	-18.0 ∓ 3.7
N(2)-C(9)-C(3)-C(2)	163.8 ∓ 1.2	-178.0 ∓ 0.5	-168.8 ∓ 1.3	176.4 ∓ 2.3
C(9)-C(3)-C(2)-C(7)	5.0 ∓ 1.9	-0.5 ∓ 0.8	-1.6 ∓ 2.1	-10.8 ∓ 3.7
C(1)-C(2)-C(7)-O(2)	111.2 ∓ 1.3	1.9 ∓ 0.8	-3.6 ∓ 2.1	113.2 ∓ 2.5
O(1)-C(4)-C(3)-C(9)	0.5 ∓ 1.9	0.1 ∓ 0.8	2.6 ∓ 2.2	15.6 ∓ 4.1
C(7)-O(2)-N(4')-C(10)	44.7 ∓ 1.7			

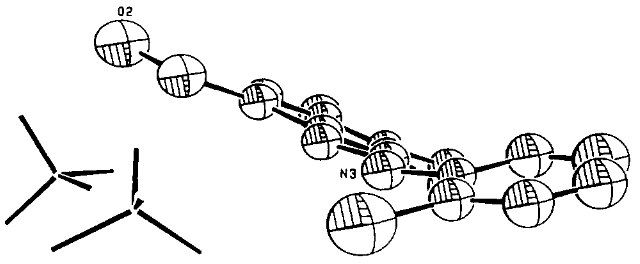


Figure 3. Perspective view of **9** with the atom-numbering scheme.

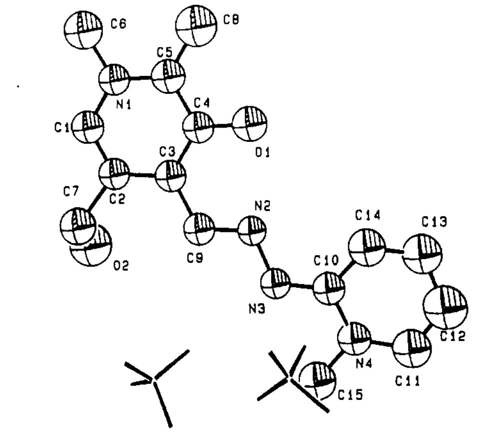


Figure 4. ORTEP drawing of **10** with the atom-numbering scheme and thermal ellipsoids at the 50% probability level.

pyridoxylidenium moiety and a 1.2-dilydropyridinium structure for the *N*-methylpyridinium moiety in the red isomer **10** ↔ **10a**. The double-bond character for the C(4)–O(1) bond in the red isomer is substantiated by the resonance at δ 170 in its ^{13}C NMR spectrum (Table I). When a solution of **9** in DMSO (yellow color) was allowed to stand in daylight for several days, its color deepened gradually to beet-red, and in its ^{13}C NMR spectrum new signals appeared at δ 16.13, 55.95, 55.48, 55.20, 54.92, 54.64, and 54.36 (compare, Table I).

Conclusion

Pyridoxal pyridylhydrazone (**1**) lends itself to N^1,N^4-dimethylation with CH_3I in two distinctly different stages. The initial step [**1** → **2a**] is rapid, generating a stable methiodide, and/or its MeOH:**2a** molecular compound **3**, whereas the following stage is very slow, giving rise to an unstable dimethiodide (**4**, not isolated) which loses 1 mol

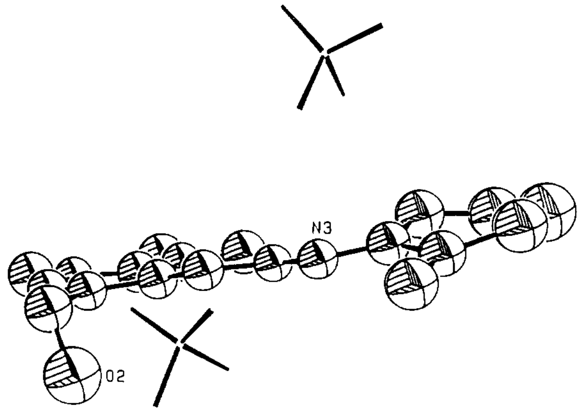


Figure 5. Perspective view of **10** with the atom-numbering scheme.

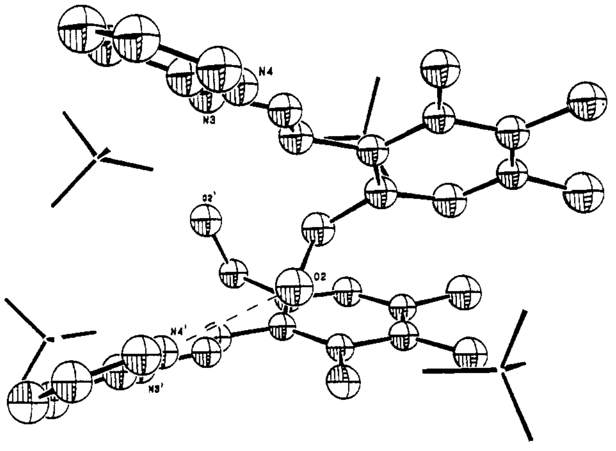


Figure 6. Perspective view of **2b** with the atom-numbering scheme.

of HI as soon as formed to yield a stable isomeric mixture of corresponding monoiodides [**5**–**6**]. Unlike the presumed dimethiodide **4**, the dimethperchlorate **9** is quite stable, arising from instantaneous displacement–addition reaction of the **5**–**6** mixture with $HClO_4$. Most interestingly, **2a** similarly generates the corresponding methperchlorate-hydroperchlorate **2b** on reaction with $HClO_4$. Comparison of crystal structures of **2b** and **9** reveals that the perchlorate counterions in their lattices are H-bonded to the respective dications via $(N^3)\text{-}H\cdots OClO_3$ and $(O^2)\text{-}H\cdots OClO_3$ contacts and that the corresponding H-bond distances increase with N-methylations in the order **2b** < **9**. Moreover, in corresponding methiodide **3**, the counterion (I^-) forms a long H-bond with the (O^2)-H group (2.51 Å),[9] whereas the respective $(O^2)\text{-}H\cdots OClO_3$ contact in **2b** is considerably shorter (1.85 Å). This explains, on the one hand, the easy $I^- + HClO_4 \rightarrow HI + ClO_4^-$ displacement, and, on the other hand, the tendency of the dimethiodide **4** to lose HI to yield [**5**–**6**].

---

(24) Avramovici-Grisaru, S.; Sarel, S.; Cohen, S.; Bauminger, R. E. *Isr. J. Chem.* **1985**, *25*, 288–292.

(25) Domiano, P.; Musatti, A.; Nardelli, M.; Pelizzi, C.; Predieri, G. *Transition Met. Chem.* **1979**, *4*, 351–354.

(26) Wilstadter, E.; Hamor, T. A.; Hoard, J. L. *J. Am. Chem. Soc.* **1963**, *85*, 1205.

(27) Capasso, S.; Giordano, F.; Mattia, C.; Mazzarella, L.; Ripamonti, A. *J. Chem. Soc., Dalton Trans.* **1974**, 2228.